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(54) Title: EMULSION PRECONCENTRATES CONTAINING CYCLOSPORIN OR A MACROLIDE

(57) Abstract

This invention provides an emulsion, e.g. microemulsion, pre-concentrate comprising a difficultly soluble active agent and a carrier medium. The active agent may e.g. be a cyclosporin or a macrolide.

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## EMULSION PRECONCENTRATES CONTAINING CYCLOSPORIN OR A MACROLIDE

The present invention relates to novel galenic compositions, in particular novel galenic compositions in which the active ingredient is a difficultly soluble active agent e.g. a macrolide, or in particular a cyclic poly-N-methylated undecapeptide, or a cyclosporin. Cyclosporins also include peptolide variants. See e.g. GB patent publications nos. 2 222 770 and 2 257 359 A and equivalents world-wide.

As discussed in the said GB patent publications, the cyclosporins present highly specific difficulties in relation to administration generally and galenic composition in particular, including in particular problems of stability, drug bioavailability, and variability in inter- and intra-patient dose response.

In order to meet these and related difficulties, in GB patent publication no. 2 222 770 and 2 257 359 A, galenic compositions are disclosed comprising a cyclosporin as active ingredient and which take the form of, inter alia, an emulsion, e.g. microemulsion, or emulsion, e.g. microemulsion, pre-concentrate. Such compositions typically comprise 1) a hydrophilic component, 2) a lipophilic component, and 3) a surfactant.

In accordance with the present invention it has now surprisingly been found that particularly stable emulsion, e.g. microemulsion, or emulsion, e.g. microemulsion, pre-concentrate galenic compositions with difficultly soluble active agents having particularly interesting bioavailability characteristics and reduced variability in inter- and intra-subject bioavailability parameters, are obtainable using at least one component selected from the group consisting of (i) triethyl citrate or acetyl triethyl citrate, (ii) polyethylene glycol glyceryl fatty acid ester, (iii) glyceryl di fatty acid ester, (iv) glyceryl mono fatty acid ester, (v) a mixture of mono-, diglycerides of fatty acids, (vi) propylene glycol mono fatty acid ester, (vii) fatty acids and alcohols, (viii) N-methyl pyrrolidone, (ix) glycerol triacetate, (x) benzyl alcohol, and (xi) alkylene polyol ether or ester, e.g. polyglycolised glycerides, hereinafter referred to as "secondary component".

In accordance with the present invention, it has surprisingly been found that such emulsion, e.g. microemulsion, systems can, in contrast to the teaching of the art, in practice indeed be prepared comprising from any of the components specified above as a second component.

5 The present invention provides in one aspect a pharmaceutical composition which is an emulsion, e.g. microemulsion, pre-concentrate comprising

- 1) a difficultly soluble active agent, and a carrier medium comprising
- 2) a second component,

10 3) a lipophilic component, and

- 4) a surfactant.

The second component is for example:

- i) triethyl citrate or acetyl triethyl citrate, and/or
- 15 ii) polyethylene glycol glyceryl fatty acid ester, e.g. mono and/or di and/or tri fatty acid ester e.g. C<sub>6</sub>-C<sub>10</sub>, e.g. C<sub>8</sub>-C<sub>10</sub>, e.g. with from 5 to 10 [CH<sub>2</sub>-CH<sub>2</sub>-O] units, e.g. 7 units, e.g. Cetiol® HE, or Labrasol®, and/or
- iii) glyceryl di fatty acid ester, e.g. C<sub>6</sub>-C<sub>16</sub>, e.g. C<sub>8</sub>-C<sub>10</sub>, e.g. C<sub>8</sub>, e.g. Sunfat® GDC-N, and/or

20 iv) glyceryl mono fatty acid ester, e.g. C<sub>6</sub>-C<sub>14</sub>, e.g. C<sub>8</sub>-C<sub>10</sub>, e.g. Imwitor® 308, or Imwitor® 310, and/or

- v) a mixture of mono-, diglycerides of fatty acids, e.g. C<sub>6</sub>-C<sub>16</sub>, e.g. C<sub>8</sub>-C<sub>10</sub>, e.g. Imwitor® 742, or Capmul® MCM, and/or
- 25 vi) propylene glycol mono fatty acid ester, e.g. C<sub>6</sub>-C<sub>12</sub>, e.g. C<sub>8</sub>-C<sub>12</sub>, e.g. Lauroglycol® 90, Sefsol® 218, or Capryol® 90, and/or
- vii) fatty acids or alcohols, e.g. C<sub>6</sub>-C<sub>20</sub>, saturated or mono- or di- unsaturated, e.g. oleic acid, oleyl alcohol, linoleic acid, capric acid, caprylic acid, caproic acid, tetradecanol, dodecanol, decanol, and/or
- viii) N-alkylpyrrolidone, e.g. N-Methylpyrrolidone, e.g. Pharmasolve®, and/or

30 ix) glycerol triacetate, e.g. Triacetin, and/or

- x) benzyl alcohol, and/or
- xi) alkylene polyol ether or ester, e.g. polyglycolised glycerides, e.g. Gelucire® 44/14

Accordingly, the present invention provides in one aspect a composition in form of an

5 emulsion or microemulsion pre-concentrate for oral administration comprising

1) a cyclosporine or macrolide, and a carrier medium comprising

2) a second component selected from the group consisting of

- (i) triethyl citrate or acetyl triethyl citrate,
- (ii) polyethylene glycol glyceryl C<sub>6</sub>-C<sub>10</sub> fatty acid ester,
- (iii) glyceryl di C<sub>6</sub>-C<sub>16</sub> fatty acid ester,
- (iv) glyceryl mono C<sub>6</sub>-C<sub>14</sub> fatty acid ester,
- (v) a mixture of mono-, diglycerides of C<sub>6</sub>-C<sub>16</sub> fatty acids,
- (vi) propylene glycol mono C<sub>6</sub>-C<sub>12</sub> fatty acid ester,
- (vii) fatty acids and alcohols,
- 15 (viii) N-methyl pyrrolidone,
- (ix) glycerol triacetate,
- (x) benzyl alcohol, and
- (xi) alkylene polyol ether or ester,

3) a lipophilic component, and

20 4) a surfactant,

with the proviso that when component 2)

(a) consists of triethyl citrate, said composition is free or substantially free of ethanol,  
and/or

(b) consists of a mixture of mono-, diglycerides of C<sub>8</sub>-C<sub>10</sub> fatty acids, said composition is  
25 free or substantially free of a C<sub>6</sub>-C<sub>12</sub> fatty acid triglyceride.

In accordance with the present invention, it has surprisingly been found that a cyclosporine or macrolide has a high solubility, e.g. a solubility of from about 20 to about 50%, in the

second component of the present invention. For example the solubility of a cyclosporin or a

30 macrolide in triethyl citrate is about 35%, in Sunfat®GDC-N about 33%, in

Lauroglycol®90 about 40%, in oleic acid about 40%, in N-methylpyrrolidone about 50%, in Labrasol about 20%, in Dodecanol about 37.5%, in Tetradecanol about 37.5%, in Sefsol®218 about 50%, in Cetiol®HE about 32.5%, in oleyl alcohol more than 20%.

5 Accordingly, the present invention provides in one aspect a composition in form of an emulsion or microemulsion pre-concentrate for oral administration comprising  
1) a cyclosporine or macrolide, and a carrier medium comprising  
2) a second component wherein component 1) has a solubility of from about 20 to about  
50%  
10 3) a lipophilic component, and  
4) a surfactant.

Preferably the composition is in the form of an "emulsion, e.g. microemulsion, preconcentrate" of the type providing o/w (oil-in-water) emulsions, e.g. microemulsions.

15 However the composition may be in the form of an emulsion, e.g. microemulsion, which additionally contains an aqueous component; preferably water.

An "emulsion, e.g. microemulsion, preconcentrate" is defined in this specification as being a composition which spontaneously forms an emulsion, e.g. microemulsion, in an aqueous  
20 medium, for example, in water, for example on dilution of 1:1 to 1:10, e.g. 1:10, or in the gastric juices after oral application.

A microemulsion is thermodynamically stable and contains dispersed particles of a mean size less than about 200 nm. Generally microemulsions comprise droplets or particles  
25 having a mean diameter of less than about 150 nm; typically less than 100 nm, generally greater than 10nm, and stable over periods in excess of 24 hours. A "microemulsion" may be a non-opaque or substantially non-opaque, alternatively it may be a translucent colloidal dispersion that is formed spontaneously or substantially spontaneously when its components are brought into contact. Further characteristics can be found in the above mentioned  
30 British patent application 2 222 770, the disclosure of which is incorporated herein by

reference.

In one aspect the present invention provides a composition according to the present invention, the relative proportion of the cyclosporine or macrolide, the second component, the lipophilic component and the surfactant in said composition being such that upon dilution with water to a ratio of 1 part by weight of said composition to 1 to 10 parts by weight of water, an oil-in-water microemulsion having particles of a mean size of less than 200 nm, is spontaneously formed.

10 In a further alternative aspect the lipophilic component may comprise 5 to 85 % by weight of the carrier medium, e.g. 10 to 85%; preferably 15 to 70 % by weight, more preferably 20 to 60 % by weight and even more preferably about 25 % by weight.

15 In a further alternative aspect the surfactant may comprise 5 to 80 % by weight of the carrier medium; preferably 10 to 70 % by weight, more preferably 20 to 60 % by weight and even more preferably about 40 % by weight.

20 In a further alternative aspect the second component may comprise 5 to 50 % by weight of the carrier medium, e.g. 10 to 50%; preferably 15 to 40 % by weight, more preferably 20 to 35 % by weight.

25 In one aspect the present invention provides a composition according to the present invention comprising the second component in an amount of 5 to 50 %, the lipophilic component in an amount of 5 to 85 %, and the surfactant in an amount of 5 to 80 % by weight of the carrier medium.

The active agent may be present in an amount by weight of up to about 20% by weight of the composition. The active agent is preferably present in an amount of 1 to 15 % by weight of the composition, for example about 2 to 10 %.

In one aspect the present invention provides a composition according to the present invention comprising the cyclosporine or macrolide in an amount of 1 to 15% by weight of the composition.

5 The difficultly soluble active agent preferably is a lipophilic drug, e.g. a cyclosporin or a macrolide. The term "difficultly soluble", as used herein, is understood to mean a solubility in water at 20°C of less than 1 e.g. 0.01 % weight/volume.

Cyclosporins to which the present invention applies are any of those having pharmaceutical utility, e.g. as immunosuppressive agents, anti-parasitic agents and agents for the reversal of multi-drug resistance, as known and described in the art, in particular Cyclosporin A (also known as and referred to hereinafter as Ciclosporin), Cyclosporin G, [0-(2-hydroxyethyl)-(D)Ser]<sup>8</sup>-Ciclosporin, and [3'-deshydroxy-3'-keto-MeBmt]<sup>1</sup>-[Val]<sup>2</sup>-Ciclosporin. Ciclosporin is preferred.

15

In one aspect the present invention provides a composition according to the present invention wherein the cyclosporine is Cyclosporin A.

The term "macrolide" as used herein, refers to a macrocyclic lactone, for example a compound having a 12- membered or larger lactone ring. Of particular interest are the "lactam macrolides", i.e., macrocyclic compounds having a lactam (amide) bond in the macrocycle in addition to a lactone (ester) bond, for example the lactam macrolides produced by microorganisms of the genus *Streptomyces* such as rapamycin, ascomycin, and FK-506, and their numerous derivatives and analogues. Such lactam macrolides have been shown to have interesting pharmaceutical properties, particularly immunosuppressive and anti-inflammatory properties.

Rapamycin is an immunosuppressive lactam macrolide that is produced by *Streptomyces hygroscopicus*. The structure of rapamycin is given in Kesseler, H., et al.; 1993; *Helv. Chim. Acta*; 76: 117. See, e.g., McAlpine, J.B., et al., *J. Antibiotics* (1991) 44: 688; Schreiber, S.L., et al., *J. Am. Chem. Soc.* (1991) 113: 7433; US Patent No. 3 929 992.

Rapamycin is an extremely potent immunosuppressant and has also been shown to have antitumor and antifungal activity. Its utility as a pharmaceutical, however, is restricted by its very low and variable bioavailability as well as its high toxicity. Moreover, rapamycin is highly insoluble, making it difficult to formulate stable galenic compositions. Numerous 5 derivatives of rapamycin are known. Certain 16-O-substituted rapamycins are disclosed in WO 94/02136, the contents of which are incorporated herein by reference. 40-O-substituted rapamycins are described in, e.g., in US 5 258 389 and WO 94/09010 (O-aryl and O-alkyl rapamycins); WO 92/05179 (carboxylic acid esters), US 5 118 677 (amide esters), US 5 118 678 (carbamates), US 5 100 883 (fluorinated esters), US 5 151 413 10 (acetals), US 5 120 842 (silyl ethers), WO 93/11130 (methylene rapamycin and derivatives), WO 94/02136 (methoxy derivatives), WO 94/02385 and WO 95/14023 (alkenyl derivatives) all of which are incorporated herein by reference. 32-O-dihydro or substituted rapamycins are described, e.g., in US 5 256 790, incorporated herein by reference.

15

Rapamycin and its structurally similar analogues and derivatives are termed collectively as "rapamycins".

Ascomycins, of which FK-506 and ascomycin are the best known, comprise another class 20 of lactam macrolides, many of which have potent immunosuppressive and anti-inflammatory activity. FK506 is a lactam macrolide immunosuppressant that is produced by Streptomyces tsukubaensis No 9993. The structure of FK506 is given in the appendix to the Merck Index, 11th ed. (1989) as item A5. Ascomycin is described, e.g., in US patent 3,244,592. Many derivatives of ascomycin and FK-506 have been synthesized, including halogenated 25 derivatives such as 33-epi-chloro-33-desoxy-ascomycin described in EP 427 680. Ascomycin, FK-506 and their structurally similar analogues and derivatives are termed collectively "ascomycins".

The macrolide may, therefore, be rapamycin or an O-substituted derivative in which the 30 hydroxyl group on the cyclohexyl ring of rapamycin is replaced by -OR<sub>1</sub> in which R<sub>1</sub> is hydroxyalkyl, hydroalkoxyalkyl, acylaminoalkyl and aminoalkyl; for example 40-O-(2-

hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin and 40-O-(2-acetaminoethyl)-rapamycin.

A preferred compound is 40-O-(2-hydroxy)ethyl rapamycin as disclosed in WO 94/09010.

5

Examples of compounds of the FK 506 class are those mentioned above. They include for example FK 506, ascomycin and other naturally occurring compounds. They include also synthetic analogues.

10 A preferred compound of the FK 506 class is disclosed in EP 427 680, e.g. Example 66a also known as 33-epi-chloro-33-desoxy-ascomycin. Other preferred compounds are disclosed in EP 465 426, and in EP 569 337, e.g. the compound of Example 71 in EP 569 337.

15 The second component may be any of components i) to xi) individually or in combination with one, two or more of the other components i) to xi). Examples of suitable second components for use in this invention are:

i) triethyl citrate or acetyl triethyl citrate. They may be obtainable by esterification of 20 citric acid and ethanol or esterification of citric acid and ethanol, followed by acetylation with acetic anhydride, respectively. Triethyl citrate or acetyl triethyl citrate are commercially available, e.g. under the trade names Citroflex® 2 or Citroflex® A-2, or triethyl citrate in a pharmaceutical grade under the name TEC-PG/N, from e.g. Morflex Inc. Particularly suitable is triethyl citrate which has molecular weight of 25 276,3, a specific gravity of 1,135-1,139, a refractive index of 1,439-1,441, a viscosity (25°) of 35,2 mPa s, assay (anhydrous basis) 99,0-100,5 %, water max. 0,25 % (Fiedler, H. P., "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", Editio Cantor Verlag Aulendorf, Aulendorf, 4th revised and expanded edition (1996), vol 1, page 371; "Handbook of Pharmaceutical Excipients", 2nd Edition, Editors A. Wade and P. J. Weller (1994), Joint publication of American 30 Pharmaceutical Association, Washington, USA and The Pharmaceutical Press,

London, England, page 540).

- ii) polyethylene glycol glyceryl C<sub>6</sub>-C<sub>10</sub> fatty acid ester. The fatty acid ester may include mono and/or di and/or tri fatty acid ester. The fatty acid constituent may include both saturated and unsaturated fatty acids having a chain length of from e.g. C<sub>8</sub>-C<sub>10</sub>. The polyethylene glycols may have e.g. from 5 to 10 [CH<sub>2</sub>-CH<sub>2</sub>-O] units, e.g. 7 units. Particularly suitable is polyethylene glycol (7) glyceryl monococoate which is commercially available, e.g. under the trade name Cetiol® HE, e.g. from Henkel KGaA. Cetiol® HE has a D. (20°) of 1,05, an acid value of less than 5, a saponification value of about 95, a hydroxyl value of about 180 and an iodine value of less than 5 (H. Fiedler, loc cit, vol 1, page 337). Further suitable is a transesterified, polyoxyethylated caprylic-capric acid glyceride as commercially available under the trade name Labrasol® from e.g. Gattefossé. Labrasol® has an acid value of max. 1, a saponification value of 90-110, and an iodine value of max. 1 (H. Fiedler, loc cit, vol 2, page 880).
- iii) glyceryl di C<sub>6</sub>-C<sub>16</sub> fatty acid ester. Diglycerides suitable for use in the compositions of the invention include both symmetric (i.e. α,α'-diglycerides) as well as assymetric diglycerides (i.e. α,β-diglycerides) and acetylated derivatives thereof. They also include both uniform glycerides (in which the fatty acid constituent is composed primarily of a single fatty acid) as well as mixed glycerides (i.e. in which the fatty acid constituent is composed of various fatty acids) any acetylated derivatives thereof. The fatty acid constituent may include both saturated and unsaturated fatty acids having a chain length of from e.g. C<sub>6</sub>-C<sub>16</sub>, e.g. C<sub>8</sub>-C<sub>10</sub>, e.g. C<sub>8</sub>. Particularly suitable is caprylic diglyceride which is commercially available, e.g. under the trade name Sunfat® GDC-N, e.g. from Taiyo Kagaku Co., Ltd. Sunfat® GDC-N has an acid value of about 0.3, a diglyceride content of about 78.8%, and a monoester content of about 8.9%.
- iv) glyceryl mono C<sub>6</sub>-C<sub>14</sub> fatty acid ester. They may be obtainable by esterification of glycerol with vegetabel oil followed by molecular distillation. Monoglycerides suitable for use in the compositions of the invention include both symmetric (i.e. β-

monoglycerides) as well as assymetric monoglycerides ( $\alpha$ -monoglycerides) and acetylated derivatives thereof. They also include both uniform glycerides (in which the fatty acid constituent is composed primarily of a single fatty acid) as well as mixed glycerides (i.e. in which the fatty acid constituent is composed of various fatty acids) any acetylated derivatives thereof. The fatty acid constituent may include both saturated and unsaturated fatty acids having a chain length of from e.g. C<sub>8</sub>-C<sub>10</sub>. Particularly suitable are caprylic or capric acid monoglycerides which are commercially available, e.g. under the trade names Imwitor® 308 or Imwitor® 310, respectively, from e.g. Condea. For example Imwitor® 308 comprises at least 80 % monoglycerides and exhibits the following additional characterising data: free glycerol max 6 %, acid value max. 3, saponification value 245-265, iodine value max. 1, water content max. 1 %. Typically it comprises 1 % free glycerol, 90 % monoglycerides, 7 % diglycerides, 1 % triglycerides (H. Fiedler, loc cit, vol 1, page 798).

15 v) a mixture of mono-, diglycerides of C<sub>6</sub>-C<sub>16</sub> fatty acids. Mixed mono-, di-glycerides suitable for use in the compositions of the invention include both symmetric (i.e.  $\beta$ -monoglycerides and  $\alpha,\alpha'$ -diglycerides) as well as assymetric mono- and di-glycerides (i.e.  $\alpha$ -monoglycerides and  $\alpha,\beta$ -diglycerides) and acetylated derivatives thereof. They also include both uniform glycerides (in which the fatty acid constituent is composed primarily of a single fatty acid) as well as mixed glycerides (i.e. in which the fatty acid constituent is composed of various fatty acids) any acetylated derivatives thereof. The fatty acid constituent may include both saturated and unsaturated fatty acids having a chain length of from e.g. C<sub>8</sub>-C<sub>10</sub>. Particularly suitable are mixed caprylic and capric acid mono- and di-glycerides as commercially available, e.g. under the trade name Imwitor® 742, from e.g. Condea. For example Imwitor® 742 comprises at least 45% monoglycerides and exhibits the following additional characterising data: free glycerol max. 2 %, acid value max. 2, saponification value 250-280, iodine value max. 1, water max. 2 % (H. Fiedler, loc cit, vol 1, page 798). Further suitable is a mono/diglyceride of caprylic/capric acid in glycerol as known and commercially available under e.g. the trade name Capmul® MCM from e.g. Abitec Corporation. Capmul® MCM exhibits

the following additional characterising data: acid value 2.5 max., alpha-Mono (as oleate) 80% min., free glycerol 2.5% max., iodine value 1 max., chain length distribution: caproic acid (C6) 3% max., caprylic acid (C8) 75% min., capric acid (C10) 10% min., lauric acid (C12) 1.5% max., moisture (by Karl Fisher) 0.5% max.

5 (manufacturer information).

vi) propylene glycol mono C<sub>6</sub>-C<sub>12</sub> fatty acid ester. The fatty acid constituent may include both saturated and unsaturated fatty acids having a chain length of from e.g. C<sub>8</sub>-C<sub>12</sub>. Particularly suitable are propylene glycol mono ester of caprylic and lauric acid as

10 commercially available, e.g. under the trade names Sefsol® 218, Capryol®90 or Lauroglycol®90, from e.g. Nikko Chemicals Co., Ltd. or Gattefossé. For example Lauroglycol®90 exhibits the following additional characterising data: acid value max. 8, saponification value 200-220, iodine value max. 5, free propylene glycol content max. 5%, monoester content min. 90%; Sefsol® 218 exhibits the following additional

15 characterising data: acid value max. 5, hydroxy value 220-280 (H. Fiedler, loc cit, vol 2, page 906, manufacturer information).

vii) fatty acids and/or alcohols. Fatty acids may be obtainable by hydrolysis of various animal and vegetable fats or oils, such as olive oil, followed by separation of the liquid

20 acids. The fatty acid/alcohol constituent may include both saturated and mono- or di-unsaturated fatty acids/alcohols having a chain length of from e.g. C<sub>6</sub>-C<sub>20</sub>. Particularly suitable are, e.g. oleic acid, oleyl alcohol, linoleic acid, capric acid, caprylic acid, caproic acid, tetradecanol, dodecanol, or decanol. For example oleyl alcohol is

commercially available under the trade mark HD-Eutanol® V from e.g. Henkel KGaA.

25 Oleyl alcohol exhibits the following additional characterising data: acid value max 0.1, hydroxy value of about 210, iodine value of about 95, saponification value max 1, D.<sup>20</sup> about 0.849, n<sub>D</sub><sup>20</sup> 1,462, molecular weight 268, viscosity (20°) about 35 mPa s (manufacturer information). Oleic acid exhibits the following additional characterising data: molecular weight 282.47, D.<sup>20</sup> 0.895, n<sub>D</sub><sup>20</sup> 1,45823, acid value 195-202, iodine value 85-95, viscosity (25°) 26 mPa s (H. Fiedler, loc cit, vol 2, page 1112; Handbook of Pharmaceutical Excipients, loc. cit, page 325).

viii) N-alkylpyrrolidone. Particularly suitable is, e.g. N-Methyl-2-pyrrolidone, e.g. as commercially available under the trade name Pharmasolve™, from e.g. International Specialty Products (ISP). N-methylpyrrolidone exhibits the following additional characterising data: molecular weight 99,1, D.<sup>25</sup> 1,027-1,028, purity (as area % by GC) (including Methyl Isomers) 99.85% min (H. Fiedler, loc. cit., vol 2, page 1004, manufacturer information).

ix) glycerol triacetate or (1,2,3)-triacetin. It may be obtainable by esterification of glycerin with acetic anhydride. Glycerol triacetate is commercially available as, e.g. Priacetin® 1580 from Unichema International, or as *Eastman* Triacetin from Eastman, or from Courtaulds Chemicals Ltd. Glycerol triacetate exhibits the following additional characterising data: molecular weight 218,03, D.<sup>20,3</sup> 1,159-1,163, n<sub>D</sub><sup>20</sup> 1,430-1,434, water content max. 0.2 %, viscosity (25°) 17.4 mPa s, acid value max. 0.1, saponification value of about 766-774, triacetin content 97% min. (H. Fiedler, loc. cit., vol 2, page 1580; Handbook of Pharmaceutical Excipients, loc. cit., page 534, manufacturer information).

x) benzyl alcohol. It may be obtainable by distillation of benzyl chloride with potassium or sodium carbonate. Benzyl alcohol is commercially available from e.g. Merck. Benzyl alcohol exhibits the following additional characterising data: molecular weight 108,14, D. 1,043-1,049, n<sub>D</sub> 1,538-1,541. (H. Fiedler, loc. cit., vol 1, page 238; Handbook of Pharmaceutical Excipients, loc. cit., page 35).

xi) alkylene polyol ether or ester. It may be suitably a C<sub>3</sub>-alkylene triol, in particular glycerol, ether or ester. Suitable C<sub>3</sub>-alkylene triol ether or ester include mixed ethers or esters, i.e. components including other ether or ester ingredients, for example transesterification products of C<sub>3</sub>-alkylene triol esters with other mono-, di- or polyols.

Particularly suitable alkylene polyol ether or ester are mixed C<sub>3</sub>-alkylene triol/poly-(C<sub>2</sub>-alkylene) glycol fatty acid esters, especially mixed glycerol/polyethylene- or

polypropylene-glycol fatty acid esters.

Especially suitable alkylene polyol ether or ester for use in accordance with the present invention include products obtainable by transesterification of glycerides, e.g. triglycerides, with poly-(C<sub>2-4</sub>alkylene) glycols, e.g. poly-ethylene glycols and, optionally, glycerol.

Such transesterification products are generally obtained by alcoholysis of glycerides, e.g. triglycerides, in the presence of a poly-(C<sub>2-4</sub>alkylene) glycol, e.g. polyethylene glycol and, optionally, glycerol (i.e. to effect transesterification from the glyceride to the poly-alkylene glycol/glycerol component, i.e. via poly-alkylene glycolysis/glycerolysis).

In general such reaction is effected by reaction of the indicated components (glyceride, polyalkylene glycol and, optionally, glycerol) at elevated temperature under an inert atmosphere with continuous agitation.

Preferred glycerides are fatty acid triglycerides, e.g. (C<sub>10-22</sub>fatty acid) triglycerides, including natural and hydrogenated oils, in particular vegetable oils. Suitable vegetable oils include, for example, olive, almond, peanut, coconut, palm, soybean and wheat germ oils and, in particular, natural or hydrogenated oils rich in (C<sub>12-18</sub>fatty acid) ester residues.

Preferred polyalkylene glycol materials are polyethylene glycols, in particular polyethylene glycols having a molecular weight of from ca. 500 to ca. 4,000, e.g. from ca. 1,000 to ca. 2,000.

Suitable alkylene polyol ether or ester thus comprise mixtures of C<sub>3-5</sub>alkylene triol esters, e.g. mono-, di- and tri-esters in variable relative amount, and poly(C<sub>2-4</sub>alkylene) glycol mono- and di-esters, together with minor amounts of free C<sub>3-5</sub>alkylene triol and free poly-(C<sub>2-5</sub>alkylene) glycol. As hereinabove set forth, the preferred alkylene triol moiety is glycetyl; preferred polyalkylene glycol moieties will be polyethylene glycol, in particular having a molecular weight of from ca. 500 to ca. 4,000; and preferred fatty acid moieties will be C<sub>10-22</sub>fatty acid ester residues, in particular saturated C<sub>10-22</sub>fatty acid ester residues.

Particularly suitable alkylene polyol ether or ester may thus alternatively be defined as:

transesterification products of a natural or hydrogenated vegetable oil and a polyethylene glycol and, optionally, glycerol; or compositions comprising or consisting of glyceryl mono-, di- and tri-C<sub>10-22</sub>fatty acid esters and polyethylene glycol mono- and di- C<sub>10-22</sub>fatty esters (optionally together with, e.g. minor amounts of free glycerol and free polyethylene glycol).

Preferred vegetable oils, polyethylene glycols or polyethylene glycol moieties and fatty acid moieties in relation to the above definitions are as hereinbefore set forth. Particularly suitable alkylene polyol ether or ester as described above for use in the present invention are those known and commercially available under the trade name Gelucire® from e.g. Gattefossé, in particular the products

- a) Gelucire® 33/01, which has an m.p. = ca. 33-38°C and a saponification value = ca. 240/260;
- b) Gelucire® 35/10, m.p. = ca. 29-34°C, saponification v. = ca. 120-140;
- c) Gelucire® 37/02, m.p. = ca. 34-40°C, saponification v. = ca. 200-220;
- d) Gelucire® 42/12, m.p. = ca. 41-46°C, saponification v. = ca. 95-115;
- e) Gelucire® 44/14, m.p. = ca. 42-46°C, saponification v. = ca. 75-95;
- f) Gelucire® 46/07, m.p. = ca. 47-52°C, saponification v. = ca. 125-145;
- g) Gelucire® 48/09, m.p. = ca. 47-52°C, saponification v. = ca. 105-125;
- h) Gelucire® 50/02, m.p. = ca. 48-52°C, saponification v. = ca. 180-200;
- i) Gelucire® 50/13, m.p. = ca. 46-41°C, saponification v. = ca. 65-85;
- j) Gelucire® 53/10, m.p. = ca. 48-53°C, saponification v. = ca. 95-115;
- k) Gelucire® 62/05, m.p. = ca. 60-65°C, saponification v. = ca. 70-90.

Products (a) to (j) above all have an acid value of max. 2. Product (k) has an acid value max. 5. Products (b), (c) and (f) to (j) above all have an iodine value of max. 3. Product (a) has an iodine value of max. 8. Products (d) and (e) have an iodine value of max. 5 or 2. Product (k) has an iodine value of max. 10.

Alkylene polyol ether or ester having an iodine value of max. 2 will generally be

preferred. As will be appreciated, mixtures of alkylene polyol ether or ester as defined may also be employed in the compositions of the invention.

Gelucire® products are inert semi-solid waxy materials with amphiphilic character.  
5 They are identified by their melting point and their HLB value. Most Gelucire® grades are saturated polyglycolised glycerides obtainable by polyglycolysis of natural hydrogenated vegetable oils with polyethylene glycols. They are composed of a mixture of mono-, di- and tri-glycerides and mono- and di-fatty acid esters of polyethylene glycol. Particularly suitable is Gelucire® 44/14 which has a nominal melting point of  
10 44°C and an HLB of 14. It is derived from the reation of hydrogenated palm kernel and/or hydrogenated palm oils with polyethylene glycol 1500. It consists of approximately 20% mono-, di- and triglycerides, 72 % mono- and di- fatty acid esters of polyethylene glycol 1500 and 8% of free polyethylene glycol 1500. The fatty acid distribution for Gelucire® 44/14 is as follows: 4-10 C<sub>8</sub>, 3-9 C<sub>10</sub>, 40-50 C<sub>12</sub>, 14-24 C<sub>14</sub>,  
15 4-14 C<sub>16</sub>, 5-15 C<sub>18</sub>. Gelucire® 44/14 exhibits the following additional characterising data: acid value of max. 2, iodine value of max. 2, saponification value of 79-93, hydroxyl value of 36-56, peroxide value of max. 6, alkalines impurities max. 80, water content max. 0.50, free glycerol content max. 3, monoglycerides content 3.0-8.0. (H. Fiedler, loc cit, vol 1, page 676; manufacturer information).

20 Although any pharmaceutically acceptable components selected from the group specified above may be used in the composition of the invention, certain components are preferred. These include triethyl citrate, acetyl triethyl citrate, N-methylpyrrolidone, glycerol triacetate, benzyl alcohol, Cetiol® HE, oleic acid, or alkylene polyol ether or ester, e.g.  
25 polyglycolised glycerides. More preferred are triethyl citrate, acetyl triethyl citrate, N-methylpyrrolidone, benzyl alcohol, Cetiol® HE, or oleic acid.

Accordingly, the present invention provides in one aspect a composition according to the present invention, wherein the second component is selected from the group consisting of  
30 (i) triethyl citrate or acetyl triethyl citrate,

- (ii) polyethylene glycol glyceryl C<sub>6</sub>-C<sub>10</sub> fatty acid ester,
- (iii) fatty acids and alcohols,
- (iv) N-methyl pyrrolidone,
- (v) glycerol triacetate,
- 5 (vi) benzyl alcohol, and
- (vii) alkylene polyol ether or ester.

In one aspect the present invention provides a composition according to the present invention wherein the second component is triethyl citrate or N-methylpyrrolidone.

10 The second component may also comprise a co-component which may be hydrophilic, e.g. selected from Transcutol (which has the formula C<sub>2</sub>H<sub>5</sub>-[O-(CH<sub>2</sub>)<sub>2</sub>]<sub>2</sub>-OH), Glycofurool (also known as tetrahydrofuryl alcohol polyethylene glycol ether) and 1,2-propylene glycol. The second component may include further hydrophilic co-components, for example lower 15 alkanols such as ethanol. These co-components will generally be present in partial replacement of other components of the second component. While the use of ethanol in the compositions is not essential, it has been found to be of particular advantage when the compositions are to be manufactured in soft gelatine, encapsulated form. This is because storage characteristics are improved, in particular the risk of active agent precipitation 20 following encapsulation procedures is reduced. Thus the shelf life stability may be extended by employing ethanol or some other such co-component as an additional ingredient of the second component. In a further alternative aspect the ethanol may comprise 0 to 60 % by weight of the second component; preferably 20 to about 55% by weight and more preferably about 40 to 50 % by weight. Small quantities of liquid polyethylene glycols may 25 also be included in the second component.

GB 2 222 770 A discloses a wide variety of lipophilic components suitable for use in the present invention. Typical examples for lipophilic components are:

30 (i) medium chain fatty acid triglycerides, e.g. C<sub>6</sub>-C<sub>12</sub>, e.g. Miglyol® 812, and/or

- (ii) mixed mono-, di-, tri-glycerides, e.g. C<sub>6</sub>-C<sub>20</sub>, e.g. C<sub>16</sub>-C<sub>18</sub>, e.g. Maisine®, and/or
- (iii) transesterified ethoxylated vegetable oils, e.g. Labrafil®, and/or
- (iv) propylene glycol mono fatty acid esters, e.g. C<sub>14</sub>-C<sub>18</sub>, e.g. propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol ricinoleate, propylene glycol stearate, and/or
- 5 (v) propylene glycol di fatty acid esters, e.g. C<sub>6</sub>-C<sub>20</sub>, e.g. C<sub>8</sub>-C<sub>12</sub>, e.g. propylene glycol dicaprylate, e.g. Miglyol® 840, or propylene glycol dilaurate, and/or
- (vi) esterified compounds of fatty acid and primary alcohol, e.g. C<sub>8</sub>-C<sub>20</sub> fatty acids and C<sub>2</sub>-C<sub>3</sub> alcohols, e.g. ethyl linoleate, and/or
- 10 (vii) mono- and/or di-glyceride, e.g. a mixture of mono- and di-glycerides with e.g. a monoglyceride of C<sub>18</sub> fatty acid as its main component, e.g. GMOrphic®-80 or Tegin® O.

Preferred lipophilic components are medium chain fatty acid triglycerides, mixed mono-, di-, tri-glycerides, and transesterified ethoxylated vegetable oils.

Accordingly, in one aspect the present invention provides a composition according to the present invention wherein the lipophilic component is selected from the group consisting of (i) medium chain fatty acid triglycerides, (ii) mixed mono-, di-, tri-glycerides, and (iii) transesterified ethoxylated vegetable oils.

In another aspect the lipophilic component may comprise a medium chain triglyceride and/or a mono-and di-glyceride or a mixture thereof.

25 As the medium chain fatty acid triglyceride in the lipophilic component a triglyceride of saturated fatty acid having 6 to 12, e.g. 8 to 10, carbon atoms can be used. Suitable medium chain fatty acid triglycerides are those known and commercially available under the trade names Acomed®, Myritol®, Captex®, Neobee®M 5 F, Miglyol®810, Miglyol®812, Miglyol®818, Mazol®, Sefsol®860, Sefsol®870; Miglyol®812 being the most preferred.

30 Miglyol®812 is a fractionated coconut oil comprising caprylic-capric acid triglycerides and

having a molecular weight of about 520 daltons. Fatty acid composition = C<sub>6</sub> max. about 3%, C<sub>8</sub> about 50 to 65%, C<sub>10</sub> about 30 to 45%, C<sub>12</sub> max 5%; acid value about 0.1; saponification value about 330 to 345; iodine value max 1. Miglyol® 812 is available from Condea. Neobee® M 5 F is a fractionated caprylic-capric acid triglyceride available from coconut oil; acid value max. 0.2; saponification value about 335 to 360; iodine value max 0.5, water content max. 0,15%, D.<sup>20</sup> 0,930-0,960, n<sub>D</sub><sup>20</sup> 1,448-1,451 (manufacturer information). Neobee® M 5 F is available from Stepan Europe.

These triglycerides are described in Fiedler, H. P., loc cit, the contents of which are hereby incorporated by reference.

In a further alternative aspect preferably monoglycerides comprise from about 25 to about 50%, based on the total weight of the lipophilic components. More preferably from about 30 to about 40% (for example 35 to 40%) monoglycerides are present.

In a further alternative aspect preferably diglycerides comprise from about 30 to about 60%, based on the total weight of the lipophilic component. More preferably from about 40 to about 55% (for example 48 to 50%) diglycerides are present.

In a further alternative aspect triglycerides suitably comprise at least 5% but less than about 25 %, based on the total weight of the lipophilic component. More preferably from about 7.5 to about 20% (for example from about 9 to 12%) triglycerides are present.

Suitable mixed mono-, di-, tri-glycerides are those known and commercially available under the trade name Maisine® from Gattefossé. They are transesterification products of corn oil and glycerol. Such products are comprised predominantly of linoleic and oleic acid mono-, di- and tri-glycerides together with minor amounts of palmitic and stearic acid mono-, di- and tri-glycerides (corn oil itself being comprised of ca. 56% by weight linoleic acid, 30% oleic acid, ca. 10% palmitic and ca. 3% stearic acid constituents). Physical characteristics are: free glycerol max 10%, monoglycerides ca. 40%, diglycerides ca. 40%, triglycerides ca.

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10%, free oleic acid content ca. 1%. Further physical characteristics are: acid value max. 2, iodine value of 85-105, saponification value of 150-175, mineral acid content = 0. The fatty acid content for Maisine® is typically: palmitic acid ca. 11%, stearic acid ca. 2.5%, oleic acid ca. 29%, linoleic acid ca. 56%, others ca. 1.5% (H. Fiedler, loc cit, vol 2, page 958; 5 manufacturer information).

In a further alternative aspect the lipophilic component may alternatively comprise e.g. a pharmaceutically acceptable oil, preferably with an unsaturated component such as a vegetable oil or fish oil.

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The lipophilic component may alternatively comprise suitable transesterified ethoxylated vegetable oils such as those obtained by reacting various natural vegetable oils (for example, maize oil, kernel oil, almond oil, ground nut oil, olive oil, soybean oil, sunflower oil, safflower oil and palm oil, or mixtures thereof) with polyethylene glycols that have an 15 average molecular weight of from 200 to 800, in the presence of an appropriate catalyst. These procedures are known and an example is described in US Patent 3 288 824. Transesterified ethoxylated corn oil is particularly preferred.

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Transesterified ethoxylated vegetable oils are known and are commercially available under the trade name Labrafil® (H. Fiedler, loc cit, vol 2, page 880). Examples are Labrafil® M 2125 CS (obtained from corn oil and having an acid value of less than about 2, a saponification value of 155 to 175, an HLB value of 3 to 4, and an iodine value of 90 to 110), and Labrafil® M 1944 CS (obtained from kernel oil and having an acid value of about 2, a saponification value of 145 to 175 and an iodine value of 60 to 90). Labrafil® M 2130 25 CS (which is a transesterification product of a C<sub>12-18</sub> glyceride and polyethylene glycol and which has a melting point of about 35 to 40°C, an acid value of less than about 2, a saponification value of 185 to 200 and an iodine value of less than about 3) may also be used. The preferred transesterified ethoxylated vegetable oil is Labrafil® M 2125 CS which can be obtained, for example, from Gattefossé, Saint-Priest Cedex, France.

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Further suitable lipophilic components for use in this invention are, e.g. propylene glycol mono- and di-fatty acid esters such as propylene glycol dicaprylate (also known and commercially available under the trade name Miglyol® 840 from e.g. Condea; H. Fiedler, loc cit, vol 2, page 1008) or propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, propylene glycol stearate and so forth (Fiedler, loc. cit., 2, p. 1277 ff).

As another lipophilic component esterified compounds of fatty acid and primary alcohol may be used. They may include esterified compounds of fatty acid having 8 to 20 carbon atoms and primary alcohol having 2 to 3 carbon atoms, for example, isopropyl myristate, isopropyl palmitate, ethyl linoleate, ethyl oleate, etc., with an esterified compound of linoleic acid and ethanol being particularly preferable.

In a further aspect as the lipophilic component a mono-and/or di-glyceride may be used. A mono- and/or di-glyceride is e.g. a mixture of glycerol mono- and di-esters of a fatty acid in which the monoglyceride content is e.g. at least 40%. It is preferable that the mono- and di-glycerides contain a monoglyceride of C18 fatty acid as its main component. Such a compound has been commercialized under the trade name GMO®AV1 (Croda Co.), ATMOS®300 (ICI Co.), GMOrphic®-80 (Eastman Co.), Tegin®O (Goldschmidt Co.), etc. For example GMOrphic®-80 (glyceryl monooleate) exhibits the following additional characterising data: monoglyceride content min. 94%, C18:1 content 75% min., peroxide value max. 2.5, C18:2 + C18:3 max. 15%, C16:0 + C18:0 + C20:0 max. 10%, water max. 2%, acid value max. 3, iodine value 65-75, saponification value 155-165, free glycerine max. 1%, hydroxyl number 300-330 (manufacturer information). Tegin® O (glyceryl oleate) exhibits the following additional characterising data: monoglyceride content 55-65%, peroxide value max. 10, water content max. 1%, acid value max. 2, iodine value 70-76, saponification value 158-175, free glycerol max. 2%, (manufacturer information).

Typically the mono/diglyceride is present at a concentration of 5-10% by weight, e.g. of the composition, of the carrier medium or of the lipophilic component.

In a further alternative aspect in the composition of the present invention, any one of the above lipophilic components, e.g. oils, alone or in combination may be used as the lipophilic component. When a mixture of any of the medium chain triglyceride and mono- and di-glyceride is used in the lipophilic component, they may be present in the mixing ratio of 5 1:0.1-1, preferably 1:0.1-0.5, on the basis of weight.

In the pharmaceutical composition of the present invention, in a further alternative aspect the constitutional ratio of the lipophilic component to cyclosporin is preferably 1-10:1 and 10 more preferably 2-6:1, on the basis of weight.

Examples of suitable surfactants for use in this invention are:

i) reaction products of a natural or hydrogenated castor oil and ethylene oxide. The 15 natural or hydrogenated castor oil may be reacted with ethylene oxide in a molar ratio of from about 1:35 to about 1:60, with optional removal of the polyethyleneglycol component from the products. Various such surfactants are commercially available. The polyethyleneglycol-hydrogenated castor oils available under the trade name Cremophor® are especially suitable. Particularly suitable are Cremophor® RH 40, which has a saponification value of about 50 to 60, an acid value less than about 1, a 20 water content (Fischer) less than about 2%, an  $n_D^{20}$  of about 1.453 to 1.457 and an HLB of about 14 to 16; and Cremophor® RH 60, which has a saponification value of about 40 to 50, an acid value less than about 1, an iodine value of less than about 1, a water content (Fischer) of about 4.5 to 5.5%, an  $n_D^{20}$  of about 1.453 to 1.457 and an 25 HLB of about 15 to 17. An especially preferred product of this class is Cremophor® RH40. Also suitable are polyethyleneglycol castor oils such as that available under the trade name Cremophor® EL, which has a molecular weight (by steam osmometry) of about 1630; a saponification value of about 65 to 70, an acid value of about 2, an iodine value of about 28 to 32 and an  $n_D^{25}$  of about 1.471.

Similar or identical products which may also be used are available under the trade names Nikkol® (e.g. Nikkol® HCO-40 and HCO-60), Mapeg® (e.g. Mapeg® CO-40h), Incrocas® (e.g. Incrocas® 40), Tagat® (for example polyoxyethylene-glycerol-fatty acid esters e.g. Tagat® RH 40; and Tagat® TO, a polyoxyethylene-glycerol-trioleate having a HLB value of 11.3; Tagat® RH 40 is preferred) and Simulsol OL-50 (PEG-40 castor oil, having a saponification value of about 55 to 65, an acid value of max. 2, an iodine value of 25 to 35, a water content of max. 8%, and an HLB of about 13, available from Seppic). These surfactants are further described in Fiedler loc. cit..

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- ii) Polyoxyethylene-sorbitan-fatty acid esters, for example mono- and tri-lauryl, palmityl, stearyl and oleyl esters of the type known and commercially available under the trade name Tween® (Fiedler, loc.cit. p.1615 ff) including the products Tween®  
20 [polyoxyethylene(20)sorbitanmonolaurate],  
15      21 [polyoxyethylene(4)sorbitanmonolaurate],  
        40 [polyoxyethylene(20)sorbitanmonopalmitate],  
        60 [polyoxyethylene(20)sorbitanmonostearate],  
        65 [polyoxyethylene(20)sorbitantristearate],  
        80 [polyoxyethylene(20)sorbitanmonooleate],  
20      81 [polyoxyethylene(5)sorbitanmonooleate],  
        85 [polyoxyethylene(20)sorbitantrioleate].

Especially preferred products of this class are Tween® 40 and Tween® 80.

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- iii) Polyoxyethylene fatty acid esters, for example polyoxyethylene stearic acid esters of the type known and commercially available under the trade name Myrj® (Fiedler, loc. cit., 2, p. 1042). An especially preferred product of this class is Myrj® 52 having a D<sup>25</sup> of about 1.1., a melting point of about 40 to 44°C, an HLB value of about 16.9., an acid value of about 0 to 1 and a saponification no. of about 25 to 35.

iv) Polyoxyethylene-polyoxypropylene co-polymers and block co-polymers, poloxamers, for example of the type known and commercially available under the trade names Pluronic®, Emkalyx® (Fiedler, loc. cit., 2, p. 1203). An especially preferred product of this class is Pluronic® F68 (poloxamer 188), having a melting point of about 52°C and a molecular weight of about 6800 to 8975. A further preferred product of this class is Synperonic® PE L44 (poloxamer 124).

v) Dioctylsodiumsulfosuccinate as known and commercially available under the trade mark Aerosol OT® from e.g. American Cyanamid Co. (Fiedler, loc. cit., 1, p. 118), or di-[2-ethylhexyl]-succinate (Fiedler, loc. cit., 1, p. 487).

vi) Phospholipids, in particular lecithins (Fiedler, loc. cit., 2, p. 910, 1184). Suitable lecithins include, in particular, soya bean lecithins.

vii) Sorbitan fatty acid esters, e.g. sorbitan mono C<sub>12-18</sub> fatty acid esters, or sorbitan tri C<sub>12-18</sub> fatty acid esters as known and commercially available under the trade mark Span® from e.g. ICI. An especially preferred product of this class is e.g. Span® 20 (sorbitan monolaurate) or Span® 80 (sorbitan monooleate) (Fiedler, loc. cit., 2, p. 1430; Handbook of Pharmaceutical Excipients, loc. cit., page 473).

viii) Polyoxyethylene mono esters of a saturated C<sub>10</sub> to C<sub>22</sub>, e.g. C<sub>18</sub> substituted e.g. hydroxy fatty acid; e.g. 12 hydroxy stearic acid PEG ester, e.g. of PEG about e.g. 600-900 e.g. 660 daltons MW, e.g. Solutol® HS 15 from BASF, Ludwigshafen, Germany.

ix) Polyoxyethylene alkyl ethers, e.g. polyoxyethylene glycol ethers of C<sub>12</sub> to C<sub>18</sub> alcohols, e.g. Polyoxy 2-, 10- or 20-cetyl ether or Polyoxy 4- or 23-lauryl ether, or polyoxyl 2-, 10- or 20-oleyl ether, or Polyoxy 2-, 10-, 20- or 100-stearyl ether, as known and commercially available under the trade mark Brij® from e.g. ICI. An especially preferred product of this class is e.g. Brij® 35 (Polyoxyl 23 lauryl ether) or Brij® 98

(Polyoxyl 20 oleyl ether) (Fiedler, loc. cit., 1, pp. 259; Handbook of Pharmaceutical Excipients, loc. cit., page 367).

Similar products which may also be used are polyoxyethylene-polyoxypropylene-alkyl ethers, e.g. polyoxyethylene-polyoxypropylene- ethers of C<sub>12</sub> to C<sub>18</sub> alcohols, e.g. polyoxyethylen-20-polyoxypropylene-4-cetylether which is known and commercially available under the trade mark Nikkol PBC® 34, from e.g. Nikko Chemicals Co., Ltd. (Fiedler, loc. cit., vol. 2, pp. 1239).

10 x) Water soluble tocopheryl polyethylene glycol succinic acid esters (TPGS), e.g. with a polymerisation number ca 1000, e.g. available from Eastman Fine Chemicals Kingsport, Texas, USA.

15 xi) Polyglycerol fatty acid esters, with e.g. from 2 to 20, e.g. 10 glycerol units. The fatty acid constituent may include both saturated and unsaturated fatty acids having a chain length of from e.g. C<sub>8</sub>-C<sub>18</sub>. Particularly suitable is e.g. decaglycerylmonolaurat or decaglycerylmonomyristat, as known and commercially available under the trade mark Decaglyn® 1-L or Decaglyn® 1-M, respectively, from e.g. Nikko Chemicals C., Ltd (Fiedler, loc. cit., vol. 2, pp. 1228).

20 xii) Polyethylene glycol glycetyl fatty acid ester. The fatty acid ester may include mono and/or di and/or tri fatty acid ester. The fatty acid constituent may include both saturated and unsaturated fatty acids having a chain length of from e.g. C<sub>12</sub>-C<sub>18</sub>. The polyethylene glycols may have e.g. from 10 to 40 [CH<sub>2</sub>-CH<sub>2</sub>-O] units, e.g. 15 or 30 units. Particularly suitable is polyethylene glycol (15) glycetyl monostearat or polyethylene glycol (15) glycetyl monooleate which is commercially available, e.g. under the trade name TGMS®-15 or TGMO®-15, respectively, e.g. from Nikko Chemicals Co., Ltd. Further suitable is polyethylene glycol (30) glycetyl monooleate which is commercially available, e.g. under the trade name Tagat® O, e.g. from Goldschmidt (H. Fiedler, loc. cit., vol. 2, p. 1502-1503).

xiii) Sterols and derivatives thereof, for example cholesterol and derivatives thereof, in particular phytosterols, e.g. products comprising sitosterol, campesterol or stigmasterol, and ethylene oxide adducts thereof, for example soya sterols and derivatives thereof, e.g. polyethylene glycol sterols, e.g. polyethylene glycol phytosterols or polyethylene glycol soya sterols. The polyethylene glycols may have e.g. from 10 to 40 [CH<sub>2</sub>-CH<sub>2</sub>-O] units, e.g. 25 or 30 units. Particularly suitable is polyethylene glycol (30) phytosterol which is commercially available, e.g. under the trade name Nikkol BPS®-30, e.g. from Nikko Chemicals Co., Ltd. Further suitable is polyethylene glycol (25) soya sterol which is commercially available, e.g. under the trade name Generol® 122 E 25, e.g. from Henkel (H. Fiedler, loc cit, vol. 1, p. 680).

It is to be appreciated that surfactants may be complex mixtures containing side products or unreacted starting products involved in the preparation thereof, e.g. surfactants made by polyoxyethylation may contain another side product, e.g. polyethylene glycol.

A surfactant having a hydrophilic-lipophilic balance (HLB) value of 8 to 17 is preferred. The HLB value is preferably the mean HLB value.

The surfactant selected preferably has a hydrophilic-lipophilic balance (HLB) of at least 10, for example Cremophor.

In one aspect the present invention provides a composition according to the present invention wherein the surfactant is selected from the group consisting of (i) reaction products of natural or hydrogenated vegetable oil and ethylene oxide, and (ii) polyoxyethylene sorbitan fatty acid esters.

Preferably the relative proportion of the second component(s), the lipophilic component and the surfactant lie within the "microemulsion" region on a standard three way plot. The compositions thus obtained are microemulsion preconcentrates of high stability that are capable, on addition to water, of providing microemulsions having a mean particle size of <

200 nm.

Standard three way plots, e.g. phase diagrams, can be generated in a conventional manner as described in e.g. GB patent publication no. 2 222 770 or WO 96/13273.

5

In a further alternative aspect, the present invention relates to a cyclosporin or macrolide preparation, which comprises

- 1) a cyclosporin or macrolide as an active ingredient;
- 10 2) a second component as specified above;
- 3) one or a mixture of two or more selected from the group consisting of an esterified compound of fatty acid and primary alcohol, medium chain fatty acid triglyceride and fatty acid monoglyceride as an oil component, and
- 4) a surfactant having an HLB (Hydrophilic Lipophilic Balance) value of 8 to 17,
- 15 e.g. in a gelatin shell containing polyethylene glycol and propylene glycol as a plasticizer.

In another aspect the present invention provides a cyclosporin or macrolide preparation, which comprises a composition containing

- 1) cyclosporin or macrolide as an active ingredient, and 2) the second component as  
20 decribed above.

Although any pharmaceutically acceptable components selected from the group specified above as secondary components may be used in such a composition, certain components are preferred. These include Sunfat®GDC-N, Lauroglycol®90, oleyl alcohol, oleic acid,  
25 alkylene polyol ether or ester, e.g. polyglycolized glycerides.

Accordingly, in another aspect the present invention provides a cyclosporin or macrolide preparation, which comprises a composition containing

- 1) cyclosporin or macrolide as an active ingredient, and 2) a second component selected  
30 from the group consisting of

- (i) glyceryl di C<sub>6</sub>-C<sub>16</sub> fatty acid ester,
- (ii) propylene glycol mono C<sub>6</sub>-C<sub>12</sub> fatty acid ester,
- (iii) fatty acids and alcohols, and
- (iv) alkylene polyol ether or ester.

5

Such a composition, which is also a composition of the invention, may optionally additionally comprise any other component as described herein, if desired in the amounts described herein.

10 The compositions may be formulated in conventional manner using recipies as disclosed in WO 97/36610 (PCT/KR/98), the contents of which are incorporated by reference, replacing the propylene carbonate by the secondary component.

If desired, polyethylene glycol which has a high boiling point, is non-volatile, and a solvent  
15 for cyclosporin, can also be present. In the composition according to the present invention, although any polyethylene glycol which can be liquified can be used, polyethylene glycol (PEG) having molecular weight of 200 to 600, particularly PEG 200, can be preferably used.

20 In the present invention, in a further alternative aspect a mixture of polyethylene glycol and the second component may be used as the component in the present invention, and can be generally combined in the ratio of 1:0.1-5, preferably 1:0.1-3, most preferably 1:0.2-2, on the basis of weight.

25 In the composition of the present invention, in a further alternative aspect the second component may be used preferably in the ratio of 0.1 to 10 parts by weight, more preferably 0.5 to 8 parts by weight, and most preferably 1 to 5 parts by weight, per 1 part by weight of cyclosporin.

30 The third component which may be used in the emulsion, e.g. microemulsion, pre-concentrate according to the present invention is a lipophilic, e.g. oil, component. As the

lipophilic, e.g. oil, component in the present invention, one or a mixture of two or more selected from the group consisting of esterified compounds of fatty acid and primary alcohol, medium chain fatty acid triglycerides (when present) and fatty acid monoglycerides can be used. The esterified compound of fatty acid and primary alcohol which can be used in the present invention may include an esterified compound of fatty acid having 8 to 20 carbon atoms and primary alcohol having 2 to 3 carbon atoms, for example, isopropyl myristate, isopropyl palmitate, ethyl linoleate, ethyl oleate, etc., with an esterified compound of linoleic acid and ethanol being particularly preferable. In addition, as the medium chain fatty acid triglyceride (when present) a triglyceride of saturated fatty acid having 8 to 10 carbon atoms can be used with caprylic/capric acid triglyceride as a vegetable oil triglyceride of saturated fatty acid being most preferably used. The fatty acid monoglyceride which can also be used as the lipophilic, e.g. oil, component in the present invention includes a monoglyceride of fatty acid having 18 to 20 carbon atoms, particularly monoglyceride of oleic acid.

15

In a microemulsion pre-concentrate according to the present invention, the lipophilic, e.g. oil, component may be used in the ratio of 1 to 10 parts by weight, preferably 2 to 6 parts by weight, per 1 part by weight of cyclosporin.

20

In a further alternative aspect preferably fatty acid monoglyceride and fatty acid ester are present as lipophilic, e.g. oil, component, e.g. in the ratio 1 : 1 to 1 : 2, e.g. 1 : 1 to 1 : 1.2.

In a further alternative aspect optionally caprylic/capric acid triglyceride is also present e.g. in a ratio to ethyl linoleate of from 1 : 0.05 to 1, e.g. 1 : 0.1 to 0.2.

25

In the oil mixture used as the lipophilic, e.g. oil, component according to the present invention, the mixing ratio of fatty acid monoglyceride: an esterified compound of fatty acid and primary alcohol: medium chain fatty acid triglyceride (when present) may be generally in the range of 1 : 0.1-5 : 0.1-10 preferably in the range of 1 : 0.1-3.0 : 0.1-3.0, on the basis of weight.

The fourth component which may be used in the composition according to the present invention is a surfactant. The suitable surfactants for use in the present invention include any of pharmaceutically acceptable surfactants having an HLB (Hydrophilic Lipophilic Balance) value of 8 to 17, which are capable of stably emulsifying the lipophilic portion of the composition comprising the cyclosporin-containing lipophilic, e.g. oil, component and the portion comprising the second component and the co-surfactant in water to form a stable microemulsion. Examples of the preferred surfactant according to the present invention include polyoxyethylene products of natural or hydrogenated vegetable oils, 5 polyoxyethylene-sorbitan-fatty acid esters, and the like, for example, Nikkol® HCO-50, Nikkol® HCO-40, Nikkol® HCO-60, Tween® 20, Tween® 21, Tween® 40, Tween® 60, Tween® 80, Tween® 81, etc. For example, a polyoxyethylene (50)- or polyoxyethylene (40)- hydrogenated castor oil which is commercialised under the trade mark Nikkol® HCO-50 or Nikkol® HCO-40, respectively, (NIKKO Chemical Co., Ltd.) and a 10 polyoxyethlyene (20) sorbitan monolaurate which is commercialised under the trade mark Tween® 20 (ICI Chemicals), having an acid value below 1, a saponification value of about 48-56, a hydroxyl value of about 45-55 and pH value (5%) of 4.5-7.0, can be preferably used.

15 In a further alternative aspect the surfactant can include any one of the above-mentioned surfactants alone or, preferably, in a combination of two or more surfactants selected from the above surfactants. In the composition according to the present invention, the surfactants can be used in the ratio of 1 to 10 parts by weight, preferably in the ratio of 2 to 8 parts by weight, per 1 part by weight of cyclosporin.

20

25 In addition, when the mixture of two surfactants, i.e. polyoxyethylene (50) hydrogenated castor oil and polyoxyethylene (20) sorbitan monolaurate is used in the composition of the present invention, the constitutional ratio of polyoxyethylene (50) hydrogenated castor oil : polyoxyethylene (20) sorbitan monolaurate is preferably in the range of 1:0.1-5, more 30 preferably in the range of 1:0.5-4, most preferably in the range of 1:0.1-0.25, on the basis of

weight.

In a further alternative aspect in the composition according to the present invention, up to four components are present preferably in the ratio of cyclosporin or macrolide: second component: lipophilic, e.g. oil, component: surfactant = 1 : 0.1- 10 : 1-10 : 1-10, and more preferably in the ratio of cyclosporin or macrolide: second component: lipophilic, e.g. oil, component : surfactant = 1 : 0.5-8: 2-6 : 2-8, by weight.

Another substance which can e.g. be used present is a hydrophilic cosurfactant e.g. a polyoxyethylene-polyoxypropylene block copolymer, poloxamer, which is liquid at room temperature. Such block copolymer has been commercialized under the trade name Pluronic® L10, L31, L35, L43, L44 (poloxamer 124), L101, 31R1, with poloxamer 124 which is pharmaceutically acceptable being preferably used as the mixture with the secondary component specified above. Poloxamer 124 is also available under trade name Lutrol® or Synperonic® PE L44. Poloxamer is a hydrophilic, high molecular surfactant having molecular weight of 2000 to 18000, which may be used as a solvent for medicinal components, lipid emulsions, ointment base, binders or coating agents for tablets, gelling agent, etc. Although the properties of poloxamers depend on their series, they are thermally stable with a flash point of 260°C. Poloxamer 124 dissolves easily in organic solvents such as propylene glycol or xylene, in contrast to other poloxamers. In addition, in comparison with all other solvents used in prior art cyclosporin formulations, poloxamer is not hygroscopic. It thus does not change the constitutional ratio by dissolution of gelatin shell, permeation or evaporation.

In one aspect the present invention provides a composition according to the present invention wherein a hydrophilic cosurfactant, e.g. a polyoxyethylene polyoxypropylene block copolymer is additionally present.

In a further alternative aspect when a mixture of the second component and polyoxyethylene-polyoxypropylene block copolymer in a liquid state at room temperature is

used in the second component in the present invention, they may be combined in the ratio of 1:0.1-5, preferably 1:0.1-3, more preferably 1:0.1-1, on the basis of weight. Typically it is present in a concentration of from 5 to 10%.

- 5 In one aspect the present invention provides a composition according to the present invention wherein the second component and the hydrophilic cosurfactant, e.g. a polyoxyethylene polyoxypropylene block copolymer, are combined in the ratio of 1 : 0.1 to 5 on the basis of weight.
- 10 In the pharmaceutical composition according to the present invention, in a further alternative aspect the ratio of cyclosporin to the hydrophilic cosurfactant is preferably in the range of 1:0.1-1, more preferably 1:0.5-0.8, on the basis of weight.

The emulsion, e.g. microemulsion, preconcentrate compositions, e.g. those in the examples 15 hereinafter, may show good stability characteristics as indicated by standard stability trials, for example having a shelf life stability of up to one, two or three years, and even longer. The microemulsion preconcentrate compositions of this invention produce stable microemulsions, e.g. for up to one day or longer, e.g. one day.

- 20 The pharmaceutical composition may also include further additives or ingredients, for example antioxidants (such as ascorbyl palmitate, butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT) and tocopherols) and/or preserving agents. In a further alternative aspect these additives or ingredients may comprise about 0.05 to 1 % by weight of the total weight of the composition. The pharmaceutical composition may also include sweetening 25 or flavoring agents in an amount of up to about 2.5 or 5% by weight based on the total weight of the composition. Preferably the antioxidant is  $\alpha$ -tocopherol (vitamin E).

Details of excipients of the invention are described in Fiedler, H. P., loc cit; "Handbook of 30 Pharmaceutical Excipients", loc cit; or may be obtained from the relevant manufacturers, the contents of which are hereby incorporated by reference.

Any carbon chain not otherwise specified herein conveniently contains 1 to 18 carbon atoms, e.g. 10 to 18 carbon atoms, when a terminal group or 2 or 3 carbon atoms when a polymer moiety.

5

It will be appreciated that the present invention encompasses

- a) in respect of component 2) any of components i) to xi) individually or in combination with one, two or more of the other components i) to xi),
- b) in respect of component 3) any of the lipophilic components specified above individually or in combination,
- c) in respect of component 4) any of the surfactants specified above, e.g. surfactants i) to xiii), individually or in combination.

The pharmaceutical compositions exhibit especially advantageous properties when administered orally; for example in terms of consistency and high level of bioavailability obtained in standard bioavailability trials, e.g. 2 to 4 times higher than emulsions. These trials are performed in animals e.g. rats or dogs or healthy volunteers using HPLC or a specific or nonspecific monoclonal kit to determine the level of the drug substance, e.g. macrolide in the blood. For example, the composition of Example 1 administered p.o. to dogs may give surprisingly high  $C_{max}$  values as detected by ELISA using a specific monoclonal antibody.

In one aspect the present invention provides a method of orally administering a pharmaceutical composition, said method comprising orally administering to a patient in need of cyclosporin or macrolide therapy a composition according to the present invention.

Pharmacokinetic parameters, for example absorption and blood levels, also become surprisingly more predictable and problems in administration with erratic absorption may be eliminated or reduced. Additionally the pharmaceutical compositions are effective with tenside materials, for example bile salts, being present in the gastro-intestinal tract. That is, the pharmaceutical compositions are fully dispersible in aqueous systems comprising such

natural tensides and thus capable of providing microemulsion systems in situ which are stable and do not exhibit precipitation of the active agent or other disruption of fine particulate structure. The function of the pharmaceutical compositions upon oral administration remain substantially independent of and/or unimpaired by the relative 5 presence or absence of bile salts at any particular time or for any given individual.

The compositions of this invention reduce variability in inter- and intra-patient dose response.

10 In one aspect the present invention provides a method of reducing the variability of bioavailability levels of a cyclosporin or macrolide for patients during cyclosporin or macrolide therapy, said method comprising orally administering an oral pharmaceutical composition according to the present invention.

15 In a further alternative aspect the invention also provides a process for the production of a pharmaceutical composition as defined above, which process comprises bringing (1) the second component; (2) the lipophilic component; and (3) the surfactant into intimate admixture, and adding the active agent, e.g. cyclosporin or the compound of the macrolide class. When required, the composition may be compounded into unit dosage form, for 20 example filling the composition into gelatine capsules.

Optionally further components or additives, in particular a hydrophilic component co-component, for example ethanol, may be mixed with components (1), (2) and (3) or with or after addition of active agent.

25 The composition may be combined with water or an aqueous solvent medium such that an emulsion, e.g. microemulsion, is obtained.

30 The present applicants also contemplate emulsion, e.g. microemulsion, preconcentrate compositions which may be free of refined fish oil and/or ethanol and/or transesterified ethoxylated vegetable oil.

It has also been found that stable compositions containing macrolides may be obtained by formulating the macrolide in an acidic environment. Compositions are understood herein to be stable when the macrolide drug substance remains substantially intact after a period of 5 days or weeks at room temperature (25°C).

The acid may be lipid soluble and/or ethanol soluble. The acid may be for example a fatty acid, e.g. oleic acid. The acid may be a carboxylic acid, for example a mono-, di- or tri-carboxylic acid, and preferably a mono- or dicarboxylic acid. The acid may comprise one or 10 more hydrophilic groups, e.g. hydroxy groups, and preferably one or two hydrophilic groups. Suitable acids for use in this invention include malonic acid, fumaric acid, maleic acid, D-malic acid, L-malic acid, citric acid, ascorbic acid, succinic acid, oxalic acid, benzoic acid or lactic acid or an acid with a similar pKa, e.g. 2-7. Preferred acids include malonic acid, oxalic acid, citric acid and lactic acid. Malonic acid is more preferred.

15 The preferred amount of acid may be determined by routine experimentation. The ratio by weight of macrolide to acid in the compositions of this invention may be up to 20:1, for example from 1:5 to 5:1, e.g. 1:1. In a further alternative aspect the acid may be present in an amount of between 0.05% and 5% by weight of the composition.

20 In a further alternative aspect the macrolide may be present in an amount of 1 to 15 % by weight of the composition.

25 The type of pharmaceutical composition is not critical. It may be solid, but it is preferably liquid. The macrolide may, for example, be formulated into an emulsion, e.g. microemulsion, preconcentrate or emulsion preconcentrate as defined above, and combined with an amount of acid. The acid-stabilised composition may be administered enterally, e.g. orally, e.g. as a capsule or drink solution, or parenterally, e.g. as an infusion concentrate. Oral administration is preferred.

The utility of all the pharmaceutical compositions of the present invention may be observed in standard clinical tests in, for example, known indications of active agent dosages giving equivalent blood levels of active agent; for example using dosages in the range of 2.5 mg to 1000 mg of active agent per day for a 75 kilogram mammal, e.g. adult and in standard animal models. The increased bioavailability of the active agent provided by the compositions may be observed in standard animal tests and in clinical trials, e.g. as described above.

The optimal dosage of active agent to be administered to a particular patient must be considered carefully as individual response to and metabolism of the macrolide compound, e.g. rapamycin, may vary. It may be advisable to monitor the blood serum levels of the active agent by radioimmunoassay, monoclonal antibody assay, or other appropriate conventional means. Dosages of a macrolide will generally range from 1 to 1000 mg per day, e.g. 2.5 mg to 1000 mg per day for a 75 kilogram adult, preferably 25 mg to 500 mg, with the optimal dosage being approximately 50 to 100 mg per day. Satisfactory results are obtained by administering about 75 mg per day for example in the form of two capsules, one containing 50 mg and one containing 25 mg; or three capsules each containing 25 mg. Cyclosporin dosages may be 25 to 1000 mg per day (preferably 50 mg to 500 mg) and the FK 506 dosage may be 2.5 mg to 1000 mg per day (preferably 10 mg to 250 mg). A daily dosage of between 0.5 and 5 mg/kg body weight/day is indicated for administration of 40-0-(2-hydroxy)ethyl rapamycin.

The pharmaceutical compositions are preferably compounded in unit dosage form, for example by filling them into orally administrable capsule shells. The capsule shells may be soft or hard gelatine capsule shells. Where the pharmaceutical composition is in unit dosage form, each unit dosage will suitably contain between 10 and 100 mg of the active agent, more preferably between 10 and 50 mg; for example 15, 20, 25, or 50 mg. Such unit dosage forms are suitable for administration 1 to 5 times daily depending upon the particular purpose of therapy, the phase of therapy and the like.

However, if desired, the pharmaceutical compositions may be in drink solution form and may include water or any other aqueous system, to provide emulsion, e.g. microemulsion, systems suitable for drinking.

5 The pharmaceutical compositions are particularly useful for treatment and prevention of the conditions disclosed at pages 40 and 41 in EP 427 680, and at pages 5 and 6 in PCT/EP93/02604, the contents of which applications are incorporated herein by reference.

The pharmaceutical compositions are particularly useful for:

10 a) treatment and prevention of organ or tissue transplant rejection, for example for the treatment of the recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants. The pharmaceutical compositions are also indicated for the prevention of graft-versus-host disease, such as sometimes occurs following bone marrow transplantation;

15 b) treatment and prevention of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronic progrediente and arthritis deformans) and rheumatic diseases; and

20 c) treatment of multi-drug resistance (MDR).

In a further aspect the present invention provides the use of a composition according to the present invention in the manufacture of a medicament for the treatment and prevention of an autoimmune or inflammatory condition or for the treatment and prevention of transplant rejection or for the treatment of multi-drug resistance.

The macrolide active agents also exhibit anti-tumour and antifungal activity and hence the pharmaceutical compositions can be used as anti-tumour and anti-fungal agents.

The contents of all the references referred to above especially the exemplified compounds are incorporated herein by reference, and each of the exemplified compounds may be used as a macrolide in the examples listed below.

5    Examples

Following is a description by way of example only of compositions of this invention. Unless otherwise indicated, components are shown in % by weight based on each composition.

- 10    Miglyol® 812 is from the Condea company, Germany.  
Labrafil® M 2125 CS, Gelucire® 44/14, Maisine®, Lauroglycol® 90 are from the Gattefossé company, France.  
Tegin® O is a representative mono-glyceride which is ca 55-65 % pure, the remainder containing diglycerides, obtainable from Goldschmitt, Essen, Germany.
- 15    Neobee® M-5 F is from Stepan Europe, France.  
GMOorphic® 80 is a representative mono-glyceride which is ca. 94% pure, the remainder containing diglycerides, obtainable from Eastman Chemicals Co., Kingsport, TN, USA.  
Synperonic® PE L44 is a representative poloxamer from ICI, UK.  
Simulsol® OI-50 is from Seppic, France.
- 20    Cremophor® RH 40 is from BASF, Germany.  
Sunfat® GDC-N is from Taiyo Kagaku Co., Japan.  
Cetiol® HE is from Henkel KGaA, Germany.

- 25    Particle size measurements are made at 20°C at a dilution of 1 ml composition in 10 to 100 ml water by photon correlation spectroscopy using, for example a Malvern ZetaSizer No. 3 from Malvern Instruments.

Example 1:

## Preparation of oral drink solutions

Compositions are made up with the following components. Some compositions are  
 5 turbid but, optionally on warming to 40°C, on dilution of 1:10 give a non-opaque, or  
 translucent liquid, which contains particles the size of which are measured by a  
 Zetasizer.

	COMPONENT	QUANTITY			
		I %	II %	III %	IV %
10	Cyclosporin A	10	10	10	10
	Triethylcitrate	10	14	5	5
15	Cremophor® RH40	40	43.75	43.11	42.5
	Synperonic® PE L44	5.71	6.00	6.07	6.07
	GMOrphic® 80	8	2	-	8.5
	Tegin® O	-	-	8.5	-
	Labrafil® M 2125 CS	5.71	6.25	5.10	6.07
20	Miglyol® 812	20.57	18.0	21.86	21.86
	Alpha-tocopherol	-	-	0.36	-
	mean Droplet size (nm)	30	36	32	29
25		V %	VI %		
	Cyclosporin A	10	10		
	N-methylpyrrolidone	9	9		
30	Simulsol® OL-50	63	54		
	Neobee® M-5 F	18	27		
	mean Droplet size (nm)	28	37		

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	VII %	VIII %	IX %	X %	
5	Cyclosporin A	10	5	10	8
	Cremophor® RH40	45	22.5	45	36
	Sunfat® GDC-N	27	13.5	-	-
	Lauroglycol® 90	-	-	36	28.8
	Propylene glycol	18	9	9	7.2
	Gelucire® 44/14	-	50	-	20
10	mean Droplet size (nm)	33	36	31	21
	XI %	XII %	XIII %	XIV %	
15	Cyclosporin A	10	8	10	8
	Cremophor® RH40	54	43.2	63	50.4
	Oleyl alcohol	18	14.4	-	-
	Oleic acid	-	-	18	14.4
20	Propylene glycol	18	14.4	9	7.2
	Gelucire® 44/14	-	20	-	20
	mean Droplet size (nm)	26	18	39	18
	XV %	XVI %	XVII %	XVIII %	
25	Cyclosporin A	10	10	10	10
	Cremophor® RH40	38.6	38.6	38.6	38.6
30	Cetiol® HE	9.5	-	-	-
	Acetyl triethyl citrate	-	9.5	-	-
	N-Methylpyrrolidone	-	-	9.5	-
	Benzyl alcohol	-	-	-	9.5
	Ethanol	9.5	9.5	9.5	9.5
35	Maisine®	32.4	32.4	32.4	32.4
	mean Droplet size (nm)	34	25	31	30

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	XIX	XX
	%	%
Cyclosporin A	10	10
5 Cremophor® RH40	38.6	38.6
Propylene glycol	9.5	9.5
Ethanol	9.5	9.5
Oleic acid	17.4	17.4
Labrafil® 1944CS	15	-
10 Labrafil® 2125 CS	-	15
mean Droplet size (nm)	29	31

These compositions may be encapsulated in hard and soft gelatine capsules.

15

Other examples may be made excluding Syneronic® PE L44, GMOrphic® 80, Tegin® O, Labrafil® M 2125 CS, Alpha-tocopherol, ethanol, propylene glycol.

Further examples may be made replacing triethyl citrate, N-Methylpyrrolidone, Sunfat® GDC-N, Lauroglycol® 90, oleyl alcohol, Cetiol® HE, acetyl triethyl citrate, benzyl alcohol, or oleic acid by any of the second components specified above.

20 The examples illustrate compositions useful for example in the prevention of transplant rejection or for the treatment of autoimmune disease, on administration of from 1 to 5 unit dosages/day at a dose of 2 to 5 mg/kg per day. The examples are described with particular reference to Ciclosporin but equivalent compositions may be obtained employing any macrolide or other active agent.

25 On visual inspection after dilution, each of the compositions forms a clear and stable microemulsion.

CLAIMS

1. A composition in form of an emulsion or microemulsion pre-concentrate for oral administration comprising
  - 1) a cyclosporine or macrolide, and a carrier medium comprising
    - 2) a second component selected from the group consisting of
      - (i) triethyl citrate or acetyl triethyl citrate,
      - (ii) polyethylene glycol glyceryl C<sub>6</sub>-C<sub>10</sub> fatty acid ester,
      - (iii) glyceryl di C<sub>6</sub>-C<sub>16</sub> fatty acid ester,
      - (iv) glyceryl mono C<sub>6</sub>-C<sub>14</sub> fatty acid ester,
      - (v) a mixture of mono-, diglycerides of C<sub>6</sub>-C<sub>16</sub> fatty acids,
      - (vi) propylene glycol mono C<sub>6</sub>-C<sub>12</sub> fatty acid ester,
      - (vii) fatty acids and alcohols,
      - (viii) N-methyl pyrrolidone,
      - (ix) glycerol triacetate,
      - (x) benzyl alcohol, and
      - (xi) alkylene polyol ether or ester,
    - 3) a lipophilic component, and
    - 4) a surfactant,  
with the proviso that when component 2)
      - (a) consists of triethyl citrate, said composition is free or substantially free of ethanol, and/or
      - (b) consists of a mixture of mono-, diglycerides of C<sub>8</sub>-C<sub>10</sub> fatty acids, said composition is free or substantially free of a C<sub>6</sub>-C<sub>12</sub> fatty acid triglyceride.
  - 25 2. A composition according to claim 1 comprising the cyclosporine or macrolide in an amount of 1 to 15% by weight of the composition.
  3. A composition according to claim 1 or 2 comprising the second component in an amount of 5 to 50 %, the lipophilic component in an amount of 5 to 85 %, and the surfactant in an amount of 5 to 80 % by weight of the carrier medium.

4. A composition according to any preceding claim, the relative proportion of the cyclosporine or macrolide, the second component, the lipophilic component and the surfactant in said composition being such that upon dilution with water to a ratio of 1 part by weight of said composition to 1 to 10 parts by weight of water, an oil-in-water microemulsion having particles of a mean size of less than 200 nm, is spontaneously formed.
5. A composition according to any preceding claim wherein the cyclosporine is Cyclosporin A.
6. A composition according to any preceding claim wherein the second component is triethyl citrate.
- 15 7. A composition according to any preceding claim wherein the second component is N-methylpyrrolidone.
8. A composition according to any preceding claim wherein the lipophilic component is selected from the group consisting of (i) medium chain fatty acid triglycerides, (ii) mixed mono-, di-, tri-glycerides, and (iii) transesterified ethoxylated vegetable oils.
- 20 9. A composition according to any preceding claim wherein the surfactant is selected from the group consisting of (i) reaction products of natural or hydrogenated vegetable oil and ethylene oxide, and (ii) polyoxyethylene sorbitan fatty acid esters.
- 25 10. A composition according to any preceding claim wherein the ratio of the cyclosporine or macrolide: second component : lipophilic component : surfactant is 1 : 0.1 to 10 : 1 to 10 : 1 to 10 on the basis of weight.
- 30 11. A composition according to any preceding claim wherein a hydrophilic cosurfactant is additionally present.

12. A composition according to claim 11 wherein the hydrophilic cosurfactant is polyoxyethylene polyoxypropylene block copolymer.
- 5 13. A composition according to claim 11 or 12 wherein the second component and the hydrophilic cosurfactant are combined in the ratio of 1 : 0.1 to 5 on the basis of weight.
14. A composition of any preceding claim in unit dosage form.
- 10 15. A method of reducing the variability of bioavailability levels of a cyclosporin or macrolide for patients during cyclosporin or macrolide therapy, said method comprising orally administering an oral pharmaceutical composition according to any preceding claim.
- 15 16. A method of orally administering a pharmaceutical composition, said method comprising orally administering to a patient in need of cyclosporin or macrolide therapy a composition according to any preceding claim.
- 20 17. The use of a composition according to any preceding claim in the manufacture of a medicament for the treatment and prevention of an autoimmune or inflammatory condition or for the treatment and prevention of transplant rejection or for the treatment of multi-drug resistance.

**INTERNATIONAL SEARCH REPORT**

International Application No PCT/EP 99/01415
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<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6 A61K9/107 A61K38/13 A61K31/435 A61K9/48
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According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 793 966 A (HANMI PHARMACEUTICAL CO LTD) 10 September 1997 see page 4, line 18 - page 5, line 28 see examples 2,4,11-14 see claims	1-3,5, 7-10,17
X	US 5 639 724 A (CAVANAK THOMAS) 17 June 1997  see column 7, line 34-49 see example 7 see claims	1-4, 8-10, 14-17
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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15 June 1999

22/06/1999

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016
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Authorized officer

La Gaetana, R

**INTERNATIONAL SEARCH REPORT**

International Application No

PCT/EP 99/01415

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 00002 A (CHONG KUN DANG CORP) 7 January 1999  see page 1, line 5-8 see page 9, line 11-27 see page 11, line 17-24 see page 17, line 24 - page 18, line 4 see page 20, line 15-20 see examples see claims ---	1-6, 8-10, 14-17
A	GB 2 278 780 A (SANDOZ LTD) 14 December 1994 ---	1,15-17
A	WO 97 36610 A (CHONG KUN DANG CORP) 9 October 1997 cited in the application see page 1, line 6-28 see page 9, line 16-21 see page 11, line 4-31 see examples see claims ---	1-17
A	FR 2 636 534 A (SANDOZ SA) 23 March 1990 cited in the application see page 13, line 2-26 see page 14, line 25-32 see examples see claims 1,2,6,7,25,29 ---	1-17
A	WO 96 13273 A (SANDOZ LTD ;SANDOZ AG (AT); SANDOZ AG (AT); COTTENS SYLVAIN (CH)); 9 May 1996 cited in the application see abstract see page 2, line 13-23 see page 12, line 16-20 see page 18, line 11-23 see examples see claims 1-3,5,6 -----	1-17

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/01415

### Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 16

because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 16

is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2.  Claims Nos.:

because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3.  Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of Invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/EP 99/01415

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0793966 A	10-09-1997	CN JP	1176826 A 10007584 A	25-03-1998 13-01-1998
US 5639724 A	17-06-1997	US US BE CH CY DE FR GB HK IT JP JP JP	5759997 A 5652212 A 1005236 A 680650 A 1886 A 4005190 A 2643262 A 2228198 A,B 149595 A 1240765 B 1888154 C 2255623 A 6011703 B	02-06-1998 29-07-1997 08-06-1993 15-10-1992 05-04-1996 23-08-1990 24-08-1990 22-08-1990 29-09-1995 17-12-1993 07-12-1994 16-10-1990 16-02-1994
WO 9900002 A	07-01-1999	AU	9465898 A	19-01-1999
GB 2278780 A	14-12-1994	GB BE CA CH DE ES FR IT JP	2315216 A,B 1008329 A 2124259 A 686761 A 4418115 A 2098180 A 2705566 A 1272992 B 7138161 A	28-01-1998 02-04-1996 28-11-1994 28-06-1996 01-12-1994 16-04-1997 02-12-1994 01-07-1997 30-05-1995
WO 9736610 A	09-10-1997	AU	3049397 A	22-10-1997
FR 2636534 A	23-03-1990	AT AT AU AU BE BG CA CH CY DE DK FI GB GR HK HU HU IE IL JP JP JP KR LU LV NL NO	403435 B 214289 A 627220 B 4140089 A 1003105 A 60525 B 1332150 A 679118 A 1711 A 3930928 A 171433 B 894342 A,B, 2222770 A,B 89100583 A,B 86593 A 212727 B 9500318 A 60764 B 91642 A 1996397 C 2121929 A 7025690 B 148748 B 87586 A 5749 A 8902315 A 180362 B	25-02-1998 15-07-1997 20-08-1992 22-03-1990 26-11-1991 28-07-1995 27-09-1994 31-12-1991 06-05-1994 22-03-1990 28-10-1996 17-03-1990 21-03-1990 31-10-1990 27-08-1993 28-10-1996 30-10-1995 10-08-1994 12-04-1994 08-12-1995 09-05-1990 22-03-1995 17-08-1998 07-05-1991 20-12-1996 17-04-1990 30-12-1996

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/01415

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR 2636534	A	PT	91731 A, B	30-03-1990
		SE	8903042 A	11-05-1990
		US	5741512 A	21-04-1998
		US	5866159 A	02-02-1999
		US	5342625 A	30-08-1994
WO 9613273	A 09-05-1996	AU	3924895 A	23-05-1996
		BR	9509496 A	30-09-1997
		CA	2200967 A	09-05-1996
		CZ	9701231 A	16-07-1997
		DE	19581805 T	16-10-1997
		EP	0787011 A	06-08-1997
		FI	970995 A	25-04-1997
		GB	2308545 A, B	02-07-1997
		GB	2327611 A, B	03-02-1999
		HU	76858 A	29-12-1997
		JP	10509699 T	22-09-1998
		NO	971898 A	24-06-1997
		NZ	295655 A	23-12-1998
		PL	319691 A	18-08-1997
		SK	52197 A	10-09-1997